CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 76005

ADMINISTRATIVE DOCUMENTS

MEMORANDUM

To: ANDA 76-005

Drug Product: Econazole Nitrate Cream, 1% Sponsor: Taro Pharmaceuticals USA, Inc.

Reference Listed Drug: Spectazole® Cream, 1%, Ortho-McNeil

Pharmaceuticals

From: Dena R. Hixon, M.D.

Associate Director for Medical Affairs

Office of Generic Drugs

Date: September 12, 2002

Background

Taro requests Formal Dispute Resolution regarding the determination by OGD that Taro's comparative clinical study fails to demonstrate the bioequivalence of Taro's econazole nitrate cream, 1% to the reference listed drug.

ANDA 76-005 was submitted on October 10, 2000. The proposed product is indicated for the treatment of tinea pedis, tinea cruris, tinea corporis, cutaneous candidiasis, and tinea versicolor.

Because the product is a topical, locally acting drug product, a 6-week comparative clinical endpoint study was conducted with 453 subjects having signs and symptoms of tinea pedis. Subjects were randomized to three treatment arms, Taro's test product, the reference product, and the vehicle as placebo. Taro's protocol included 4 weeks of treatment and a follow-up evaluation 2 weeks after discontinuation of treatment. Three study endpoints were evaluated: "Clinical" cure was defined as a total score of 2 or less and a severity score of no more than 1 for any of 6 clinical parameters at the 6 week visit. "Mycological" cure was defined as negative 10% KOH prep and negative fungal culture at both 4 and 6 weeks. "Therapeutic" cure, defined as a combination of both clinical and mycological cure, was a secondary endpoint in the protocol.

The OGD bioequivalence review focused on the criteria of therapeutic cure (clinical and mycological cure <u>at the 6 week visit</u>) for the evaluable population, consistent with prior reviews of topical antifungal agents. The therapeutic cure rate at 6 weeks was 63% for Taro's product and 50.6% for Ortho's product and 21.3% for the placebo. The 90% confidence interval (-0.02, +0.26) did not meet the established bioequivalence criteria of \pm 20%. The reviewer concluded that the study fails to demonstrate bioequivalence of Taro's Econazole Nitrate Cream 1% with the reference listed drug, Spectazole ® Cream 1%.

The firm asserts that the bioequivalence criteria for systemically bioavailable drug products is not appropriate for topical, locally acting drug products and that FDA is applying rigid and inappropriately stringent statistical criteria to assess the study results. They also suggest that bioequivalence for the sorts of drugs under consideration for which there are no dose-related safety issues would be more appropriately defined as non-inferiority in concert with no significant superiority.

Taro did not submit the study protocol for review and comment by OGD prior to conducting the clinical endpoint study described above. The firm had previously submitted ANDA 75-673 for Clotrimazole/Betamethasone Dipropionate Cream, USP 1%/0.05% with a similar study protocol that had likewise not been presented for review and comment prior to the study. That ANDA was reviewed and approved based upon the accepted criteria of therapeutic cure at 6 weeks, even though the protocol-defined endpoint was clinical cure at 6 weeks and mycological cure at both 4 and 6 weeks. The sponsor was not advised of the criteria used for that review and is now surprised that the same protocol-defined endpoints have not been accepted.

Taro proposes that statistical significance, and not the currently accepted 90% confidence interval limits, should be used in evaluating results of clinical endpoint studies for bioequivalence.

Discussion

The sponsor has conducted bioequivalence trials in 453 subjects to evaluate a clinical endpoint that is considerably more variable than the standard PK endpoints that are commonly studied in far fewer subjects for products that act through systemic exposure. Treatment with the proposed product resulted in a slightly better cure rate at the follow up visit than that achieved by the reference product. There is no known or theoretical safety concern and no increase in adverse reactions with the proposed product.

Given that there is more variability in clinical endpoints than in standard PK bioequivalence study results, the 1990 draft guidance deserves further re-evaluation. Meanwhile, it would be inconsistent and inappropriate to change the bioequivalence criteria for an individual product.

The endpoints accepted by OGD to date are consistent with the 1990 draft guidance, which states that "the evaluation of therapeutic equivalence will be based on the percentages of patients in each group that have a clinical cure and a mycological cure," and further that "while these comparisons should be evaluated at the end of treatment and at the two week follow up visits, primary weight will be given to the two week follow up evaluation in determining if bioequivalence has been established."

The firm's proposal to define mycological cure as negative KOH and fungal cultures at both end of treatment and at the two week follow up visit is acceptable and consistent with the draft guidance, as the criteria are more stringent and include the required emphasis on the follow up evaluation. Incorporating results at both 4 and 6 weeks should

minimize false negative culture results and confirm cures. Therapeutic cure, including the clinical cure component, should be defined at the same time points as mycological cure. Therefore, if the definition of mycological cure incorporates results from both weeks 4 and 6, then results from both weeks 4 and 6 should also be incorporated into the definition of clinical and therapeutic cures.

The FDA statistician has calculated the following 90% confidence intervals for the cure rates with the Taro product compared to the Ortho product using these revised definitions and the modified evaluable population: mycological cure (-0.139, 0.131), clinical cure (-0.155, 0.124), and therapeutic cure (-0.102, 0.180). These confidence intervals are all within the acceptable range for bioequivalence. Furthermore, both products show a statistically significant difference from placebo for clinical, mycological, and therapeutic cures at 6 weeks and at both 4 and 6 weeks.

Conclusion

Using definitions of clinical, mycological, and therapeutic cure that incorporate results at both 4 weeks (end of treatment) and 6 weeks (2 weeks post-treatment follow up), the study submitted to ANDA 76-005 on October 10, 2000 is adequate to demonstrate bioequivalence of Taro Pharmaceuticals USA, Inc.'s Econazole Nitrate Cream, 1% with the reference listed drug, Ortho McNeil Pharmaceuticals' Spectazole® Cream, 1%.

9/12/02

Dena R. Hixon, M.D.

Associate Director for Medical Affairs

Office of Generic Drugs

REVIEW OF PROFESSIONAL LABELING DIVISION OF LABELING AND PROGRAM SUPPORT LABELING REVIEW BRANCH

ANDA Number: 76-005 Date of Submission: October 10, 2000

Applicant's Name: Taro Pharmaceuticals USA, Inc. Established Name: Econazole Nitrate Cream, 1%

Labeling Deficiencies:

- 1. CONTAINER (15 g, 30 g, 85 g, 120 g) Include the degrees centigrade, 30°C, with your storage temperature recommendation.
- 2. CARTON (15 g, 30 g, 85 g, 120 g) See CONTAINER comment.
- INSERT
 - a. DESCRIPTION Enhance the clarity of the structural formula.
 - b. CLINICAL PHARMACOLOGY (Microbiology) Revise this subsection to be in accord with the image below which is from the currently approved labeling for Spectazole – The R.W. Johnson Pharmaceutical Research Institute; approved in draft February 24, 1995.

CLINICAL PHARMACOLOGY:

After topical application to the skin of normal subjects, systemic absorption of econazole nitrate is extremely low. Although most of the applied drug remains on the skin surface, drug concentrations were found in the stratum corneum which, by far, exceeded the minimum inhibitory concentration for dermatophytes. Inhibitory concentrations were achieved in the epidermis and as deep as the middle region of the dermis. Less than 1% of the applied dose was recovered in the urine and feces.

Microbiology: Econazole nitrate has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section.

Dermatophytes		Yeasts
Epidermophyton floccosum	Trichophyton mentagrophytes	Candida albicans
Microsporum audouini	Trichophyton rubrum.	Malassezia furfur
Microsporum canis	Trichophyton tonsurans	
Microsporum gypseum		•

Econazole nitrate exhibits broad-spectrum antifungal activity against the following organisms in vitro, but the clinical significance of these data is unknown.

Dermatophytes	Yeasts
Trichophyton verrucosum	Candida guillermondii
	Candida parapsilosis
	Candida tropicalis

c. HOW SUPPLIED - See CONTAINER comment.

Please revise your labels and labeling, as instructed above, and submit in final print.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes -

http://www.fda.gov/cder/ogd/rld/labeling review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wpr. Peter Rickman Acting Director

Division of Labeling and Program Support

Øffice of Generic Drugs

Center for Drug Evaluation and Research

APPROVAL SUMMARY

REVIEW OF PROFESSIONAL LABELING DIVISION OF LABELING AND PROGRAM SUPPORT LABELING REVIEW BRANCH

ANDA Number:

76-005

Date of Submission:

August 20, 2001 (Amendment)

December 6, 2001 (Amendment)

Applicant's Name:

Taro Pharmaceuticals USA, Inc.

Established Name: Econazole Nitrate Cream, 1%

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval): Do you have 12 Final Printed Labels and Labeling? Yes

CONTAINER LABELS: (15 g, 30 g, 85 g, and 120 g tubes)

Satisfactory as of August 20, 2001 submission (Vol. A3.1, Attachment 15)

CARTON LABELING: (15 g, 30 g, 85 g, and 120 g)

Satisfactory as of August 20, 2001 submission (Vol. A3.1, Attachment 15)

PATIENT PACKAGE INSERT LABELING (Code #PK-3310-0, Issued September 2001, 0901-0): Satisfactory as of December 6, 2001 submission (Vol. A4.1)

BASIS OF APPROVAL:

Patent Data - NDA 18-751

No	Expiration	Use Code	Use	File
		There are no unexpired patents for this product.		

Exclusivity Data For NDA 18-751

Codolous		Use	. Description	Labeling Impact
Code/sup	Expiration	Code	<u> </u>	 Labeling impact
			There is no unexpired exclusivity for this product	,

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Spectazole Cream, 1%

NDA Number: 18-751

NDA Drug Name: Econazole Nitrate Cream, 1%

NDA Firm: The R.W. Johnson Pharmaceutical Research Institute

Date of Approval of NDA Insert and supplements #011: February 24, 1995

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Side-by-side comparison with RLD labeling

Basis of Approval for the Carton Labeling: Side-by-side comparison with RLD labeling

Other c	ommeni	ts: N	lone
---------	--------	-------	------

703

NOTES/QUESTIONS TO THE CHEMIST:

Taro is proposing to package this product in a package size that differs from provide stability data supporting this new package size?

REVIEW OF PROFESSIONAL LABFLING CHECK LIST

Established Name	Yes	No	NA
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 24		Х	
is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			Χ.
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	· ·
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?		· ·	Х
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.	X		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.			
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?	 		X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		х	
Is the strength and/or concentration of the product unsupported by the insert labeling?	1	X.	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		;	X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		Х	
Are there any other safety concerns?		X	
Labeling			
is the name of the drug unclear in print or tacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?	1.		X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		×	
Labeling(continued)	Yes	No	NA.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		Х	
is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		·	X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			Х
Has the firm failed to describe the scoring in the HOW SUPPLIED section?	+		x
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?	+	X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?	 	X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?	1	X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?	 	X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		 	x
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?	+	 	X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)	+	 	x

USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)		
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?	Х	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?	X	
Does USP have labeling recommendations? If any, does ANDA meet them?	Х	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	Х	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)		
Insert labeling references a food effect or a no-effect? If so, was a food study done?	Х	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.	Х	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	-	

FOR THE RECORD:

 Labeling review based on the approved labeling of NDA 18-751 for the RLD (Spectazole Cream - The R.W. Johnson Pharmaceutical Research Institute; approved in draft February 24, 1995. Since the entire insert labeling was not included with the supplement, labeling from J&Js's website, the PDR and the approval letter were used until labeling can be obtained from HFD-540.

2. Patents/Exclusivities

Patent Data - NDA 18-751

No	Expiration	Use Code	Use	File
		There are no unexpired patents for this product.		

Exclusivity Data For NDA 18-751

Code/sup	Expiration	Use Code	Description	Labeling Impact
			There is no unexpired exclusivity for this product	

3. Storage Conditions:

Not subject of a USP monograph RLD – Store below 86°F ANDA – Store below 86°F(30°C)

4. Product Line:

The RLD packages its product in 15 g, 30 g, and 85 g tubes

Taro proposes to package its products in 15 g, 30 g, 85 g, and 120 g white enamel coated, epoxy/phenolic internal lacquered aluminum tubes with white piercing tipped caps. (Vol. B1.1, Section XIII, Page 997)

5. Inactive Ingredients:

There appear to be no discrepancies between the listing of inactives (B1.1, Section VII, page 855).

6. Manufacturer of Finished Product

Taro Pharmaceuticals Inc. 130 East Drive Bramalea, Ontario Canada, L6T 1C3

7. Bioequivalence Issues: Pending

Date of Review:
December 27, 2001

August 20, 2001 (Amendment)
December 6, 2001 (Amendment)

Primary Reviewer:

Date:

| 2/27/0 |
| Date:

| 12/27/0 |
| Date:
| 12/27/0 |
| Date:
| D

TELEPHONE MEMO

TO:

Kalpana Rao

Taro Pharmaceuticals 914-345-9001 x 298

REF#

ANDA 76-005

FROM:

Krista Scardina

DATE:

18 June 2001

SUBJECT:

Econazole Nitrate Cream, 1%

REQUESTED BY: Mary Fanning

waiy ranning

The firm was asked to submit the following information:

- 1. Case Report Forms for the 2 patients (159 and 763) who were classified as protocol violations since the report does not specify the basis for this determination.
- 2. Information on medication use during the study as well as data collected on compliance.